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Findings from bipolar disorder genome-wide association studies replicate in a Finnish bipolar family-cohort

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Recently, genome-wide association studies (GWAS) have yielded replicable findings and confirmed previous candidate genes as important factors in non-psychiatric diseases such as type 2 diabetes.1 However, there has been more controversy of GWAS studies related to bipolar (BP) spectrum disorder and other complex psychiatric traits. Part of the controversy is explained by a small effect of single single nucleotide polymorphisms (SNPs) to the development of these diseases and the difficulty of detecting rare alleles. Also, the diagnosis and lack of measurable physiological parameters in these diseases is still challenging the field.2 However, three GWAS studies on BP have been published up to date.1,3,4 These recent studies identified several candidate genes but shared only a small amount of findings. 5 In this replication study, our aim has been to elucidate the role of these variants in Finnish BP families.

We have analysed the strongest associating SNPs from the Welcome Trust Case Control Consortium,1 from Baum *et al.* and from meta-analysis5 in a Finnish family-based study sample of BP. From Baum *et al.* and WTCCC, we selected the best associating SNPs (*P*-value < 0.0001 and $P < 0.000054$, respectively) and those SNPs that are located at lithium pathway genes. Altogether we genotyped 26 SNPs in 723 individuals from 180 families with type I bipolar disorder, using Sequenom iPLEX technology.6,7 We studied the patients' phenotypic association using dichotomized diagnostic classes of bipolar type I disorder and broad mood disorder spectrum as assessed with *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition criteria. Single SNP and haplotype association analyses were carried out using FBAT8 coding the unaffected family members as unknown.

Interestingly, we could confirm findings for six associating SNPs: DFNB31, rs10982256, ($P < 0.01$), SORCS2, rs4411993, rs7683874 and rs10937823, ($P < 0.01$), SCL39A3, rs4806874, ($P < 0.05$) and diacylglycerol kinase-η (DGKH), rs9315885, ($P < 0.05$).3,5 However, no association was seen with SNP rs420259 of PALB2 gene ($P = 0.4$), which yet mapped the strongest associating genome region in WTCCC study.1 The association results in Finnish bipolar families are presented in Table 1.

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Interestingly, four SNPs that associated in this study were allelic replications, which further supports the role of these genes as probable players in BP even though the functional variants still remain to be identified. SORCS2 is expressed in the central nervous system, where this receptor is related to act upon synaptic stimuli.9 All three SNPs from SORCS2 represented the same signal as judged by haplotype analysis. The best signal in this study comes from DFNB31, which remained significant also after correction for multiple testing. It is widely expressed in central nervous system where it might enhance synaptic transmissions. Mutation of this gene cause recessive form of hearing loss.1,3 It also gave more significant association in broad mood disorder spectrum making it a candidate gene also in other psychiatric diseases. In addition, the replicated signal from DGKH is also worth noting because of its crucial role in phosphatidylinositol pathway in lithium signalling.10 Though many of the tested SNPs did not associate in our study, they may still contribute to the development of this disease. Part of this may be explained by genetic heterogenity between the Finnish and other European populations or the requirement of large sample size needed to find these variants.

It has been challenging to obtain replicable findings in psychiatric diseases using traditional candidate gene linkage and association studies.2 However, the recent GWA studies have now provided us with new tools for finding the genes that affect these conditions, as shown in this study and thus give us new insight to the pathways and brain systems that are involved in development of psychiatric disorders and give us targets for development of medication.

References

1. WTCCC. Nature. 2007; 447:661–678. [PubMed: 17554300]
2. Craddock N, O'Donovan MC, Owen MJ. Mol Psychiatry. 2008; 13:649–653. [PubMed: 18504426]
3. Baum AE, Akula N, Cabanero M, Cardona I, Corona W, Klemens B, et al. Mol Psychiatry. 2008; 13:197–207. [PubMed: 17486107]
4. Sklar P, Smoller JW, Fan J, Ferreira MA, Perlis RH, Chambert K, et al. Mol Psychiatry. 2008; 13:558–569. [PubMed: 18317468]
5. Baum AE, Hamshere M, Green E, Cichon S, Rietschel M, Noethen MM, et al. Mol Psychiatry. 2008; 13:466–467. [PubMed: 18421293]
6. Palo OM, Antila M, Silander K, Hennah W, Kilpinen H, Soronen P, et al. Hum Mol Genet. 2007; 16:2517–2528. [PubMed: 17673452]
7. Soronen P, Silander K, Antila M, Palo OM, Tuulio-Henriksson A, Kieseppä T, et al. Biol Psychiatry. 2008; 64:438–442. [PubMed: 18466879]
8. Horvath S, Xu X, Lake SL, Silverman EK, Weiss ST, Laird NM. Genet Epidemiol. 2004; 26:61–69. [PubMed: 14691957]
9. Hermey G, Plath N, Hübner CA, Kuhl D, Schaller HC, Hermans-Borgmeyer I. J Neurochem. 2004; 88:1470–1476. [PubMed: 15009648]
10. Berridge MJ. JAMA. 1989; 262:1834–1841. [PubMed: 2674489]

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Table 1

Genotyping results of associated SNPs

						MAF		*BP (N = 214)*		*Broad mood (N = 298)*	
Gene	***SNP***	***Chr***	***Replication***	***Major allele***	***Minor allele***	***Cases***	***Unaffected***	**Z**	**P**	**Z**	**P**
1p31	rs2989476	1	WTCCC	G	C	0.951	0.376	-0.135	0.892598	0.149	0.81483
TCF7L1	rs6732834	2	Baum (sup)	C	T	0.072	0.07	0.245	0.806607	0.3	0.764179
DPP10	rs1375144	2	WTCCC	A	G	0.480	0.434	-1.056	0.290897	-0.775	0.438352
CMTM8	rs4276227	3	WTCCC	C	T	0.191	0.203	-0.308	0.758132	-0.415	0.678012
LAMP8	rs683395	3	WTCCC	A	G	0.084	0.081	0.377	0.705905	1.056	0.290942
SORCS2	rs4411993	4	Baum *et al.*	C	T	0.191	0.162	2.475	**0.006045**	2.455	**0.014106**
SORCS2	rs7683874	4	Baum *et al.*	G	A	0.124	0.114	2.492	**0.012695**	2.612	**0.008991**
SORCS2 [a]	rs10937823	4	Baum *et al.*	C	T	0.112	0.999	2.864	**0.004187**	2.827	**0.004703**
6p21.1	rs6458307	6	WTCCC	C	T	0.290	0.283	0.550	0.582353	1.03	0.303185
GABBR2	rs3802477	9	Baum (sup)	T	C	0.048	0.056	-0.531	0.595076	-0.399	0.689954
DFNB31 [a]	rs10982256	9	WTCCC	C	T	0.441	0.414	2.584	**0.009756**	3.226	**0.001255**
DFNB31	rs942518	9	Baum *et al.*	A	G	0.052	0.052	1.165	0.243882	0.657	0.511144
JAM3	rs10791345	11	Baum (meta)	G	A	0.228	0.254	0.422	0.672997	0.664	0.506783
DGKH [a]	rs9315885	13	Baum *et al.*	T	C	0.368	0.411	-1.818	0.069024	-0.709	0.478431
DGKH	rs1170191	13	Baum *et al.*	G	A	0.202	0.252	-1.469	0.141857	-1.345	0.178471
NALCN	rs9513877	13	Baum *et al.*	G	A	0.347	0.321	0.202	0.840305	-0.195	0.845672
TDRD9	rs11622475	14	WTCCC	C	T	0.292	0.249	-0.278	0.781012	0.142	0.886769
A2BP1	rs10500336	16	Baum *et al.*	A	G	0.102	0.125	-1.275	0.202177	-0.512	0.60885
A2BP2	rs7204975	16	Baum *et al.*	C	T	0.214	0.217	-0.708	0.478677	-0.238	0.811732
PALB2	rs420259	16	WTCCC	A	G	0.308	0.32	-0.880	0.378765	-0.406	0.6847
16q12.2	rs1344484	16	WTCCC	T	C	0.431	0.415	-1.014	0.310807	-0.063	0.949499
PLCG2	rs4586425	16	Baum *et al.*	C	T	0.262	0.231	0.280	0.779841	0.03	0.976307
NXN	rs2360111	17	Baum *et al.*	C	T	0.432	0.418	1.233	0.217596	0.893	0.37204
FZD2	rs4792948	17	Baum *et al.*	C	T	0.128	0.146	1.241	0.21447	1.715	0.086303
SLC39A3 [a]	rs4806874	19	Baum (meta)	A	G	0.414	0.372	-2.116	**0.034354**	-1.129	0.258847
CDC25B	rs3761218	20	WTCCC	T	C	0.264	0.287	0.952	0.340967	0.231	0.816992

Abbreviations: BP, bipolar; Chr, chromosome; MAF, minor allele frequency; SNP, single nucleotide polymorphism; WTCCC, Wellcome Trust Case Control Consortium.

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Bold values signify $P < 0.05$.

[a]The associating allele is same as in previous association studies.